**The instinctive human fear of radioactivity is not irrational . . .
it is also so universal and so enduring that it is a political fact of life.**
Peter Pringle and James Spigelman
The Nuclear Barons, 1981

Forum

Of Mice and Humans

Japanese scientists have, for the first time, successfully introduced an intact human chromosome into mouse embryonic stem (ES) cells. This advance, reported in the June 1997 issue of *Nature Genetics*, may make possible medical treatments that are now technically difficult or impossible, and may allow for studies of the function of genes in their native genetic environment.

Kazuma Tomizuka of the Central Laboratories for Key Technology at Kirin Brewery Company, Ltd., in Yokohama, Japan, and nine coauthors described how intact human chromosomes were transferred into the ES cells through a process called microcell-mediated chromosome transfer (MMCT) and used to produce chimeric mice.

The group introduced chromosome 2, 14, or 22 individually into mice. Chromosomes 14 and 22 remained separate and intact, retaining all the genetic information normally contained in those chromosomes. A fragment of chromosome 2 not only remained stable and separate in the genome, but also was passed through the germline to four generations of descendants, showing that the fragment can successfully move through the normal cellular processes of mitosis and meiosis in the mouse cells.

The Japanese scientists chose chromosomes 2, 14, and 22 because these chromosomes contain the genes necessary to produce the heavy and light peptide chains that make up human antibodies. They hoped to produce antibodies that would contain only human proteins, without any proteins of mouse origin. Previous studies have transferred genes to produce human antibodies in mice but, because insufficient genetic material was transferred, the antibodies were created from the genes of both mice and humans. Such antibodies would therefore contain proteins derived from mice as well as humans and, when injected into human patients during gene therapies, would be recognized by the body as foreign and rejected. Theoretically, because MMCT allows for the transfer of whole chromosomes, antibodies produced using this method would contain no mouse proteins, thus circumventing a daunting hurdle in the clinical use of antibodies.

The group showed that the transferred chromosomes are retained intact and express the proteins that are encoded on the chromosome. Not only did the mice produce antibodies (which recombined normally) and use them to launch an attack on an injected antigen, they also expressed the genes mostly in the thymus and spleen, exhibiting tissue-appropriate expression.

Foreign genes have previously been introduced into cells and living organisms by the transfer of yeast artificial chromosomes (YACs) into cells or by using bacterial vector systems. However, this is the first time an entire human chromosome has been transferred into an organism. Tomizuka's group transferred 50 times more DNA than had been previously introduced into a mouse. "The pieces we wanted to use were two to three megabases [long]," said Mitsuo Oshimura, one of the authors of the paper and a scientist in the department of molecular and cell genetics at Tottori University. "That's too big for a YAC."

"Why were we first?" said Oshimura. "Because no one else tried. We, too, were surprised it worked. It was encouraging that YACs can be used, but we jumped into trying to put the whole chromosome in."

By introducing entire chromosomes, the group is providing the human genes the genetic environment they need to be expressed normally in the foreign mouse cells. Genes not only require their own code to be expressed but may also require many regulatory sequences, which sometimes reside thousands of base pairs away from the expressed gene on the chromosome.

Patrick Vojta, a former postdoctoral fellow at the NIEHS whose graduate and postgraduate work included MMCT, said, "This work has taken what was previously a common cell culture model and brought it up to the level of the organism." There is much speculation as to other future uses of this method. It may be useful in studying the normal function of genes. "The ability to make a better mouse [model], one that more closely resembles the human, is a very important goal," said Carl Barrett, scientific director of the NIEHS and a leading expert on MMCT. "The paper by Tomizuki [and colleagues] will greatly facilitate our ability to express human genes in the mouse and thereby improve experimental models of human disease."

The group's next paper, which has been submitted but not yet published, will report the successful simultaneous transfer of two chromosomes into the genome of one mouse, said Oshimura. The researchers plan to extend the work by crossing mice containing human chromosomes with knockout mice that cannot produce mouse antibodies. It is hoped that the resulting offspring will make only human antibodies.

Currently, the group plans to transfer chromosome 21 to produce a mouse model of Down's syndrome, which is caused by trisomy 21. They also hope to transfer the chromosomes containing the human P450 metabolic genes to study the toxicity of chemical metabolites produced by humans when exposed to environmental toxins.

Irradiating Ourselves

Everyone living in the contiguous 48 states during U.S. atomic testing in the 1950s was exposed to radioactive iodine, and these exposures could ultimately cause 10,000–75,000 excess cases of thyroid cancer, according to information released in August by the National Cancer Institute (NCI).

The highest doses of iodine-131, the NCI reports, were probably received by people living in certain areas of Idaho and Montana during the testing. While the average thyroid dose of radiation to the 160 million Americans who were exposed was around 2 rads, the dose to people living in Meagher County, Montana, and Custer, Gem, Blaine, and Lemhi counties in Idaho was between 12 and 16 rads. The average individual in the United States today is exposed to about 0.1 rad per year of cosmic radiation.

The NCI also noted that for certain subcategories of the population, the thyroid dose was probably substantially higher than the average for the area in which they lived. Children between the ages of 3 months and 5 years received doses that exceeded the average by a factor of 3–7, and individuals who drank unprocessed milk or goat's milk shortly after the tests also received substantially higher doses.

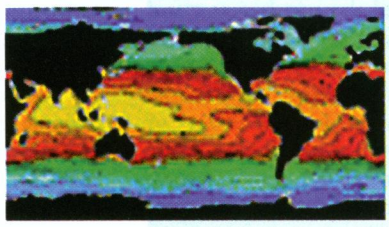
The conclusions were drawn from 14

years of research conducted by the NCI in response to a 1982 congressional mandate to evaluate the health effects of iodine-131 that was released during 90 nuclear weapons tests in Nevada. That mandate, contained in Public Law 97-414, directs the Secretary of the Department of Health and Human Services to provide estimates of iodine-131 exposure to the U.S. population, to estimate the doses received by individuals, and to assess the risk of thyroid cancer from these doses.

The full NCI report, which will be released 1 October 1997 will fulfill only the first two of these three directives, but information accompanying the executive and technical summaries of the report, which were released on 1 August 1997, provides rough preliminary estimates of cancer risk. The NCI report explains that in order for such estimates to be refined, further research must be done on the effects of internal radiation doses on the thyroid gland. The National Academy of Sciences' Institute of Medicine has been directed to further study cancer risks to individuals and to recommend public health measures to deal with these risks.

The 90 nuclear tests conducted at the Nevada Test Site, mainly in the years 1952, 1953, 1955, and 1957, resulted in the release of 150 million curies of iodine-131. Because iodine-131 decays with a half-life of 8 days, most exposure took place during the first two months following the tests.

For most people, the NCI reports, the major exposure route was consumption of milk from cows that had been grazing on pasture land contaminated by iodine-131. Because of iodine-131's short half-life, individuals who drank milk shortly after it was taken from a family cow had higher exposures than those that drank milk that had been processed and shipped from a dairy farm. Other exposure routes considered in the NCI study are inhalation of contaminated air and ingestion of leafy vegetables, goat's milk, cottage cheese, and eggs.



The NCI will release its full 1,000-page report on the exposures in October, along with a 100,000-page version that includes the full data set with annexes and subannexes. The full report will contain exposure estimates categorized by age, gender, and dietary history for each of the 3,071 counties in the contiguous United States, allowing individuals to estimate their personal levels of exposure. The NCI plans to make the information available on CD-ROM and on the Internet.

EHPnet

Surfing the Pacific

The breadth and complexity of the earth's oceans are astounding. Near the surface they are the scene of human battles over commercial fisheries, and in their deepest depths they are home to what may be the most primitive creatures in existence. They give rise to large weather patterns such as El Niño that affect the health of many land-based populations, and to small eddies that transport fish larvae from hatching grounds into the open waters.

Much of life on earth depends on the ever-changing physical characteristics of oceans, but studying their complex, interrelated systems has often proved difficult. To make understanding these important ecosystems easier, the Pacific Marine Environmental Laboratory (PMEL) of the National Oceanic and Atmospheric Administration (NOAA) has compiled much of its data into Internet pages, accessible on the World Wide Web from the PMEL home page located at http://www.pmel.noaa.gov/pmelhome.html.

PMEL "theme pages" deal with topics including large-scale phenomena like the El Niño Southern Oscillation, seismicity in the ocean, and life in the Bering Sea, and provide links to PMEL data relevant to each subject, allowing users to see the practical applications of PMEL research. For example, pages linked to the El Niño theme page not only explain how this tropical ocean weather phenomenon affects fisheries and rainfall around the world, but also show how the PMEL sea level analyses and drifting ocean buoy data help scientists predict when the next El Niño event will occur.

Many of the data sets that are linked to the El Niño theme page are presented using Java applets, which allow a quick and smooth interface between the user and PMEL computers. The Tropical Atmosphere Ocean Buoy Array page, for example, provides a map of the ocean with dots marking the position of each buoy. Simply moving the mouse pointer over one of these dots will cause the most current data collected by that buoy to be displayed in a box below. Animated ocean temperature maps and time series of data can also be viewed using Java. For users with Web browsers that are not Java-enabled, all of these data are also available through standard HTML pages and anonymous ftp.

The Bering Sea and North Pacific Ocean theme page provides links to both PMEL data and off-site data that are being used to understand and model the complex relationships between the northern ocean environment and the biota that thrive there. Pages of links are provided via this theme page to data on atmospheric conditions such as wind, pressure, and precipitation; oceanic conditions such as sea temperature, turbulence, and salinity; and life-forms such as phytoplankton, zooplankton, and fish. Abstracts of PMEL articles on each of these subjects can also be obtained through pull-down menus below the links.

Another theme page provides access to research on seismic events in the Pacific Ocean, with earthquake epicenters in geologically active segments of the northeast and eastern equatorial ocean marked on detailed topographic maps. A theme page that deals with research conducted by the NOAA ship *Ka'imimoana* is continuously updated via a satellite link to the ship, which also allows visitors to the PMEL site to send e-mail to the ship's crew. Also linked to the PMEL's home page are theme pages that deal with other ways the laboratory is using satellites to analyze the ocean and efforts being made to recover and utilize old data.

Research that does not fit into any of the theme pages is accessible through the PMEL data link on the home page. For example, users can access information on how the PMEL is using underwater telephone cables to measure currents off the coast of Florida. Other links on the home page access an expansive list of PMEL publications and a calendar of upcoming oceanography-related workshops. The PMEL World Wide Web site is large, complex, and full of information—much like the oceans the laboratory's researchers aim to understand.